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Right internal thoracic artery versus radial artery as the second best arterial conduit. Insights from a meta-analysis of propensity-matched data on long term survival

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Abbreviations

CABG: coronary artery bypass grafting

CI: Confidence interval

HR: Hazard ratio

LCA: left coronary artery

OR: Odds ratio

PSM: propensity score matching

RA: radial artery

RCA: right coronary artery

RCT: randomized controlled trial

RITA: right internal thoracic artery

UNM: unmatched

Abstract (*Word count: 250)*

Objective(s): We conducted a meta-analysis of propensity score matching (PSM) studies comparing long term survival of patients receiving right internal thoracic artery (RITA) versus radial artery (RA) as second arterial conduit for coronary artery bypass grafting (CABG).

Methods: A literature search was conducted using MEDLINE, EMBASE and Web of Science to identify relevant articles. Primary end-point was long term mortality. Secondary end-points were: operative mortality and incidence of sternal wound infection **and repeat revascularization. Binary event were pooled with DerSimonian and Laird method. For time to event outcomes, estimates of log hazard ratio (HR) and standard errors obtained were combined using the generic inverse-variance method.**

Results: A total 8 PSM studies were finally selected including 15374 patients (RITA=6739; RA=8635) with 2992 matched pairs for final comparison. Mean follow-up time ranged from 45 to 168 months. **When compared to RA, RITA was associated with a lower risk reduction of late death (HR 0.75; 95%CI 0.58-0.97; P=0.028) and repeat revascularization (HR 0.37; 95%CI 0.16-0.85; P=0.03). On the other hand, RITA did not increase operative mortality (OR 1.53; 95%CI 0.97; 2.39; P=0.07). RITA was associated with an increased risk of sternal wound complication when pedicled harvesting was used (OR 3.18; 95%CI 1.34-7.57) but not with skeletonized harvesting (OR 1.07; 95%CI 0.67-1.71).**

Conclusions: The present PSM data meta-analysis suggests that the use of the RITA when compared to the RA was associated with superior long term survival and freedom from repeat revascularization with similar operative mortality and

incidence of sternal wound complication when skeletonized harvesting technique was used.

Central message: Compared to radial artery, right internal thoracic artery is associated with superior long term survival when used as second arterial conduit in patients undergoing CABG.

Perspective Statement: The choice of the right internal thoracic artery or radial artery as second conduit of choice in coronary artery bypass graft surgery remains controversial. **The present propensity matched data meta-analysis showed when compared with the radial artery that the right internal thoracic artery is associated with superior long term survival and freedom from repeat revascularization with similar operative mortality and incidence of sternal wound complication when skeletonized harvesting technique was used.**

Central picture. By pooling data from eight propensity score matching studies, the right interal thoracic artery (RITA) was found to be associated with a 25% risk reduction of late death when compared to radial artery.

Despite increasing recognition that multiple arterial conduits improve long-term outcomes following coronary artery bypass grafting (CABG) [1], the quest for the second best arterial conduit to supplement the left internal thoracic artery continues [2]. In particular, whether the use of the right internal thoracic artery (RITA) confers a survival advantage when compared to the radial artery (RA) still needs to be determined [3]. **The lack of clear evidence, the potentially increased sternal wound complication rate and the perceived technical complexity by using bilateral internal thoracic arteries often result in the RA as the preferred second conduit of choice [1].** To date, only a single randomized controlled trial (RCT), the Radial Artery Patency and Clinical Outcomes (RAPCO) study [3] has been published in the literature, largely underpowered to detect any difference in long term survival between RITA and RA groups. Propensity score matching (PSM) based analysis of observational data is emerging as an attractive alternative in view of paucity of evidence from RCT, and can be relied upon as evidence when RCTs are not possible [4]. Several large PSM studies comparing RITA versus RA have been recently published with inconclusive findings [5-12]. Here, we propose to overcome potential limitations related to underpowered individual reports, by conducting a meta-analysis of PSM studies comparing RITA versus RA as second arterial conduit on long term survival in patients undergoing CABG.

Methods

Search strategy and selection of studies

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [13] (see Supplementary Table 1 for the PRISMA checklist). A literature search was conducted using MEDLINE, EMBASE and Web of Science to identify relevant articles on January

2016. Observational studies included in the present meta-analysis met the following criteria: (i) patients underwent first time isolated CABG;(ii) comparison of long term survival of patients receiving RITA versus RA as second arterial conduit was made; (iii) propensity score matching was used to account for non-random allocation to treatment (RITA vs RA). Non-English language, review articles and editorials were excluded. Search terms used the controlled vocabularies of MEDLINE and EMBASE alone or in combination with text words including 'radial artery', 'right internal thoracic artery', 'right internal thoracic artery', 'bilateral internal thoracic artery', 'bilateral internal thoracic artery', 'propensity score' and 'propensity score matching'. Two reviewers (U.B. and M.G.) independently reviewed the results on titles and abstracts to determine whether the study met the inclusion criteria. In case of disagreement, an agreement was negotiated. In case of several publications with overlapping study populations, the largest sample size study with longest follow-up available was selected. The quality of included studies was assessed with the Newcastle-Ottawa scale for observational studies [14]. The total score was 9 stars, and the quality was graded as low level (<6 stars) or high level (≥6 stars).

Data extraction

Microsoft Office Excel 2010 (Microsoft Corp., Redmond, WA, USA) was used for data extraction. Data extraction of all included studies was performed independently by two researchers (U.B. and A.D.F). In case of disagreement about extracted data, an agreement was negotiated. Study design, study period, country and centre where the study was conducted, unmatched and matched sample size, designated target for experimental graft, PSM methods, completeness of follow-up and follow-up duration were documented. The following patient characteristics in the unmatched and matched groups were also registered: age, female gender,

diabetes mellitus, reduced left ventricular ejection fraction (as defined by authors), chronic obstructive pulmonary disease, renal impairment (as defined by authors) and predicted operative risk according to the Euroscore or STS score [15].

Long-term mortality was the primary end point of our meta-analysis. Secondary end-points were operative mortality, incidence of sternal wound complication and repeat revascularization. Time to event outcomes (long-term mortality and repeat revascularization) were extracted as hazard ratios and its variance form the matched sample. When only the graphed survival curves and the number of persons at risk at each of several time points in the PSM comparison groups were provided, the method of Williamson et al. [16] was used to obtain the hazard ratio estimates and variance. **Binary end-points (operative mortality and sternal wound complication) were extracted as event and sample size in the matched groups.**

Statistical analysis

Meta-analysis was pre-specified to use a random effects model because of the anticipated variety in study designs and populations thus a more conservative value was obtained. Binary event data RITA versus RA cohorts were computed as odds ratio and associated 95% confidence intervals and pooled with the method of DerSimonian and Laird [17]. For time to event outcomes, estimates of log hazard ratios and standard errors obtained were combined using the generic inverse-variance method. I^2 statistic was used to estimate the percentage of total variation across studies that is due to heterogeneity rather than chance. Suggested thresholds for heterogeneity were used, with I^2 values of 25–49%, 50–74% and ≥75%, indicative of low, moderate and high heterogeneity [18]. Publication bias was evaluated using visual inspection of funnel plot asymmetry and Begg and Mazumdar rank correlation test [19].

For the primary outcome, secondary analyses were conducted including leave-one-out sensitivity analyses and radial (or Galbraith) plot to assess the influence of outliers. Radial plot is designed to assess the extent of heterogeneity between studies. The y-axis shows the (log-transformed) effect size divided by its standard error (z score) and the inverse of the standard error on the x-axis. Each study is represented by a single dot, and a regression line runs centrally through the plot. Parallel to the regression line, at a 2-standard-deviation distance, 2 lines create an interval in which most dots would be expected to fall if the studies were estimating a single fixed parameter. A line projected from (0, 0) through a particular point within the plot onto this arc indicates the value of the observed outcome for that point. In addition, estimates obtained from PSM were pooled with those from available RCTs. Finally, to investigate external validity of the main analysis, estimates obtained from all unmatched populations (including observational non-PSM studies) were pooled. Subgroup analysis was conducted according to the target selected for the second arterial conduit (left coronary artery system only versus both left and right coronary artery systems) and to the internal thoracic artery harvesting technique. A subgroup analysis according to the internal thoracic artery harvesting technique was also conducted for the incidence of sternal wound complication. Statistical analysis was conducted using *meta* package for R (meta: General Package for Meta-Analysis. R package version 4.3-2. https://CRAN.R-project.org/package=meta).

Results

Selected studies

From 673 abstracts, we selected 15 full-text articles fitting our selection criteria. After evaluating the full-text articles, we excluded 6 observational studies **[20-25]** which did not perform PSM adjustment and **one RCT, the RAPCO trial [3] (Supplementary Table 2).** A total 8 PSM studies [5-12] were finally selected for the systematic review and meta-analysis. **Of note, the study population in the RAPCO trial [3] was also part of a large Australian multicentre registry [10] included in the present analysis.** An outline of the systematic review process is depicted in Figure 1. **An overview of PSM studies is summarized in Table 1 and Table 2 (variables included for PSM are summarized in Supplementary Table 3).** Overall, selected studies reported on 15374 patients (RITA=6739; RA=8635) with 2992 matched pairs for final comparison. **Risk factors distribution before and after matching for each study is reported in Table 3. Overall, PSM and unmatched populations presented a similar preoperative risk factors distribution. Newcastle-Ottawa scale confirmed high quality level for all PSM studies included in the analysis (Supplementary Table 4).**

Primary analysis on long term mortality

All studies reported on long term mortality comparison. Mean follow-up time ranged from 45 to 168 months. RITA group was associated with a statistically significant 25% risk reduction of late death when compared to RA group (HR 0.75; 95%CI 0.58-0.97; P=0.028; Figure 2; **Central picture**). We found moderate heterogeneity among studies (I^2=66.5%;95%CI 29.1%-84.2%). No publication bias were found (P=0.62; **Supplementary Figure 1).**

Operative mortality

All studies selected reported on operative mortality comparison although different definitions were adopted (Supplementary Table 5). Operative mortality rate ranged from 0.7% to 4.03% and from 0% to 3.4% in the RITA and the RA groups respectively and pooled estimate showed no significant difference between the two groups (OR 1.53; 95%CI 0.97; 2.39; P=0.07; Figure 3A). There was no significant heterogeneity among studies (I^2=0%; 95%CI 0%-56.5%). No publication bias were found (P=0.80; **Supplementary Figure 2A).**

Sternal wound complications

All but one [5] studies reported on sternal wound complications in the matched population although different definitions were adopted. These ranged from 1.7% to 3.2% and from 0% to 3.6% in the RITA and the RA groups respectively. Pooled estimate showed a trend towards a higher incidence of sternal wound complications in patients receiving the RITA (OR 1.50; 95%CI 0.86; 2.60; P=0.15; Figure 3B). **Low to moderate heterogeneity among studies was found (I^2=43.4%;95%CI 0%-76.2%). Subgroup analysis according to the internal thoracic artery harvesting technique showed that RITA was associated with a significant 3-fold increased risk of sternal wound complication when pedicled harvesting only was used [9,11] (OR 3.18; 95%CI 1.34-7.57) whilst the two groups were comparable in studies where a skeletonized approach was used [6-8,10,12] (OR 1.07; 95%CI 0.67-1.71) (Test for subgroup differences P =0.12).** No publication bias were found (P=0.17; **Supplementary Figure 2B).**

Repeat revascularization

Three studies only reported on the incidence of repeat revascularization in the matched population [5,7,8]. Pooled estimate showed that RITA was associated with

a significantly lower risk of repeat revascularization (HR 0.37; 95%CI 0.16-0.85; P=0.03; Figure 3C). However, heterogeneity was significantly higher between the three studies (I^2 = 74.7%; 95%CI 15.9%-92.4%). No significant publication bias were found (P=0.11; Supplementary Figure 2C).

Secondary analyses on long term survival

The forest plots of the leave-one-out sensitivity analysis (Figure 4 left) and the radial plot (Figure 4 right) showed that there were no significant outliers in the meta-analysis. The survival advantage by preferring the RITA was also confirmed by pooling PSM studies with the RAPCO trial (HR 0.77; 95%CI 0.60-0.99; P=0.04) (Supplementary Figure 3). All but 2 PSM studies [7,12] and all but 2 studies among non-PSM observational cohorts [24,25] reported on late mortality in the unmatched population. Pooled estimates from unmatched populations supported a survival benefit from the RITA over the RA (HR 0.73; 95%CI 0.54-0.98; P=0.03; Supplementary Figure 4). Subgroup analysis showed that when compared to RA, the use of RITA was associated with better long term survival when used to graft either the left coronary artery system only (HR 0.81;95%CI 0.60-1.10) or both the left and right coronary systems (HR 0.56; 95%CI 0.38-0.81; Test for subgroup differences P =0.12; Supplementary Figure 5) and no significant differences were found between studies where skeletonized harvesting [5-8,10,12] (HR 0.67; 95%CI 0.50-0.89) versus pedicled harvesting only [9,11] was used (Test for subgroup differences P=0.22).

Discussion

The main findings of the present PSM data meta-analysis is that when compared with the RA, the use of the RITA was associated with superior long term survival and lower incidence of repeat revascularization in patients undergoing CABG with an additional arterial conduit. The use of the RITA was associated with superior survival regardless of the target coronary location.

Moreover, the use of the RITA instead of the RA did not significantly increase operative mortality and when harvested as skeletonized conduit, the RITA did not increase the risk of sternal wound complication compare to the RA. When harvested as a pedicle, RITA was found to significantly increase the risk of sternal wound complication.

In spite of a slow initial adoption, multiple arterial grafting is now widely advocated by the cardiovascular community [1]. The use of both RITA and RA has been showed to be associated with better long term survival when compared to the traditional strategy with a single internal thoracic artery and additional saphenous vein grafts [9]. Contention still remains, on whether the use of the RA as second arterial conduit achieves the same long-term benefits as that documented with the use of RITA [10]. The lack clear evidence, the potentially increased sternal wound complication rate and the perceived technical complexity by using bilateral internal thoracic arteries often result in the RA as the preferred second conduit of choice [1]. The only randomized direct comparison in the literature is the Radial Artery Patency and Clinical Outcome (RAPCO) [3] which randomized 196 patients to the RITA and 193 patients to the RA. At midterm follow-up no significant differences in terms of angiographic patency and clinical outcome were found. However, the trial was largely underpowered to detect significant differences in survival between the two groups. On the other hand, results of larger observational studies on the argument have been discordant and inconclusive [9-10].

Along with large registry data, meta-analysis of PSM data is emerging as an attractive alternative in view of paucity of evidence from RCT [4] and overcomes potential limitations related to underpowered individual studies. By pooling data from PSM studies, we found that the use of the RITA was associated with a 25% risk reduction of late mortality. When compared to the RA, the use of the RITA was associated with better survival regardless of the target coronary location, thus supporting previous reports [26,27]. The main reason for the long-term benefit of the RITA has been attributed to its higher capacity than of nitric oxide than the RA which might be responsible for the inferior long-term graft patency [28]. The superiority of RITA over RA in terms of long term survival is also supported by a recent network meta-analysis of RTC [2] which found RITA to be associated with a 27% absolute risk reduction for late (>4 years) functional graft occlusion when compared with the RA. **Of note, we found a significant heterogeneity for late mortality among studies. Different risk profile of study populations might partially explain such variability. The study by Ruttmann et al. [8] reported the highest effect size in a relatively younger population (mean age 57), with relatively low prevalence of female gender (10%) and diabetes mellitus (20%). The other extreme is the study by Tsuneyoshi et al. [12] which reported the lowest effect size in a relatively older population (mean age 68) with a higher prevalence of female gender (~20%) and diabetes mellitus (~50%). Also Tranbaugh et al. failed to show any benefit from the RITA. Of note, in their study the prevalence of female gender and diabetes was relatively high (~23% and 36% respectively). It has been proposed that low risk patients with prolonged life expectation are more likely to present a survival benefit from the use of the RITA. In fact its beneficial impact on survival may be delayed by as much as a 7 to 10 years but persists beyond that time period; thus, it may be less appreciated in older patients with coexistent**

morbidities and limited life expectancy [29-31]. Another possible explanation for heterogeneity among studies is the use of different surgical technique. In the study by Ruttmann [8], the RITA was preferentially used as in situ graft through the transverse sinus whilst in the study by Trambough [11], it was used as a Y graft in most cases. The latest configuration is more technically demanding and expose to higher rates of competitive flow which can potentially increase graft failure [32] though no definitive data are available to confirm this finding [33]

We found that when harvested as a skeletonized conduit, the use of the RITA was associated to a similar rate of postoperative sternal complications observed in those receiving the RA. However, when harvested as a pedicled, the RITA was associated with a 3-fold increased risk of sternal wound infection. Skeletonized harvesting has been consistently demonstrated to minimize the risk of sternal wound complication in patients receiving bilateral internal thoracic arteries [34-36] in particular in those with diabetes mellitus [35-36].

The present analysis has intrinsic limitations. Propensity matching can adjust only for measurable and included variables and we cannot exclude a selection bias based on non-measurable “eye-ball” variables (with the RITA reserved to healthier and better patients). **Moreover the use of propensity matching while increases the internal validity of studies, limits the ability to generalize findings. Only 39% of the overall study population in the present meta-analysis was included in the propensity-matched groups. Moreover, data on diabetic patients were not reported separately. Therefore we could not draw conclusion on the superiority of the RITA in terms of late survival in this high risk subgroup. Finally the different authors used different PSM models so that the homogeneity of the included population cannot be regarded as optimal. In particular, three out of 8 studies included [5,9,12] did not**

specify whether the methods used for comparison accounted for matched pairs and only one study [11] tested the non-violation of proportional hazard assumption.

In conclusion the present PSM data meta-analysis suggests that, when compared to the RA the use of the RITA can be associated with superior long term survival and lower incidence of repeat revascularization. However, this benefit might be less relevant in high risk subgroups such as older, female and diabetic patients. In particular, specific data on diabetic population are not available. In this group, the RA should be considered as a valid option also taking into account the increased risk of sternal wound complication in case of bilateral internal thoracic arteries harvesting. Skeletonized harvesting should be strongly recommended when the RITA is preferred over RA as this technique minimizes the risk of sternal wound complication.

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Table 1. Overview of propensity score matching studies included in the primary analysis

Author [ref]	Year publication	Country	Centres	Study Period	Target	Outcomes of interest reported	ITA-H
Navia [5]	2014	Argentina	Institute Cardiovascular of Buenos Aires	2003-2011	LCA /RCA	Hospital mortality, deep sternal wound infection (not in the matched population) Late survival, readmission/reintervention.	Skeleton
Pevni [6]	2016	Israel	Tel Aviv Medical Center	1996-2010	LCA only	Operative mortality, deep sternal infection, late survival	Skeleton
Raja [7]	2014	United Kingdom	Harefield Hospital	2001-2013	LCA /RCA	Operative mortality, sternal wound inferction, late mortality, repeat revascularization	Pedi/Skel
Ruttmann [8]	2011	Austria	Innsbruck Medical University	2001-2010	LCA only	Operative mortality, Sternal dehiscence, late survival, repeat revascularization	Pedi/Skel
Schwann [9]	2014	United States	University of Toledo, Mercy Saint Vincent (Toledo, OH), Yale New Haven Hospital	1987-2011	LCA only	30-day mortality, deep sternal infection, late survival	Pedicled
Shi [10]	2015	Australia	Austin Hospital, Epworth Hospital Richmond, Epworth Eastern Hospital, Knox Hospital, Royal Melbourne Hospital, St Vincent's Hospital Melbourne, Warringal Hospital	1995-2010	LCA only	30-day mortality, deep sternal wound infection, late survival.	Pedi/Skel
Tranbaugh [11]	2013	United States	Beth Israel Medical Center, St. Luke's Roosevelt Hospital Center	1995-2009	LCA only	Surgical mortality, sternal wound infection, late survival, Symptom-driven cardiac catheterization	Pedicled
Tsuneyoshi [12]	2015	Japan	Kurashiki Central Hospital	2000-2013	LCA only	Hospital death, deep sternal wound infection, late survival	Skeleton

LCA: left coronary artery ; RCA: right coronary artery; ITA-H: internal thoracic artery harvesting

Table 2. Overview of propensity score matching methods in studies included in the primary analysis

First Author [ref]	UNM RITA n	UNM RA n	PSM RITA n	PSM RA n	PSM methodology	Methods for comparison accounting for matched groups	Follow-up (months)	Completeness of follow-up	Proportional Hazard Assumption	PSM-HR for mortality provided
Navia [5]	1447	253	149	149	Five-digit 1:1 matching without replacement	Not specified (log-rank)	Mean 45 IQR: 24-66	94.1%	Not reported	No
Pevni [6]	1329	389	268	268	1:1 matching with a 5% difference as a matching threshold value	Yes (Cox stratified on matched pairs)	Mean 168 95%CI 161-179	97%	Not reported	Yes
Raja [7]	747	779	510	510	greedy 1:1 matching with caliper of width of 0.20 StDev of the logit of the PS	Yes (Klein and Moeschberger)	Mean 96 IQR 36-124	100%	Not reported	Yes
Ruttmann [8]	277	724	277	277	2-digit 1:1 matching without replacement	Yes (Cox stratified on matched pairs)	Mean 58 range: 3 -112	Not reported	Not reported	Yes
Schwann [9]	641	3095	551	551	nearest-neighbor matching caliper of width ±1% difference in PS	Not specified (Cox regression)	Range: 3 – 189	100%	Not reported	Yes
Shi [10]	912	1909	591	591	greedy 1:1 matching with a fixed caliper width of 0.05.	Yes (Klein and Moeschberger)	NA	100%	Not reported	No
Tranbaugh [11]	1154	1334	528	528	nearest-neighbor, caliper-constrained matching technique	Not specified (Cox regression)	RITA 102±55 RA 108±52	Not reported	Reported	Yes
Tsuneyoshi [12]	232	152	118	118	1:1 matching. Method not reported	Not specified (log-rank)	RITA 73 RA 94	91%	Not reported	No

UNM: unmatched; PSM: propensity score matching; RITA: right internal thoracic artery; RA: radial artery; UNM: unmatched; HR: hazard ratio; LCA: left coronary artery; RCA: right coronary artery

Table 3. Risk factors distribution in the unmatched and matched population in studies included in the primary analysis

		Unmatched							Propensity score matched						
		Age (mean)	**Female**	**DM**	**LVD**	**COPD**	**RD**	**Operative Risk**	**Age (mean)**	**Female**	**DM**	**LVD**	**COPD**	**RD**	**Operative Risk**
Navia	RITA	63±9	8%	26%	20%	NR	4%	2.7±2.3*	68±8	17%	30%	30%	NR	6%	3.9±2.4*
[5]	RA	69±10	12%	33%	35%		6%	4.8±3.3*	67±10	19%	32%	30%		4%	3.9±2.6*
Pevni	RITA	18%††	22%	38%	8%	5%	8%	5.8±3.2*	18%††	31%	54%	4%	12%	8%	6.05±3.3*
[6]	RA	36%††	36%	61%	6%	15%	12%	7.5±4.1*	22%††	31%	52%	4%	8%	8%	5.90±3.17*
Raja	RITA	60	11%	16%	13%	8%	2%	NR	62	12%	21%	15%	7%	1%	NR
[7]	RA	62	16%	31%	18%	7%	1%		62	15%	25%	17%	7%	1%	
Ruttmann	RITA	57±10	10%	21%	20%	33%	3%	2.3±2.6*	57±10	10%	21%	20%	33%	3%	2.3±2.6*
[8]	RA	60±10	14%	24%	24%	20%	1%	2.8±2.3*	58±9	10%	22%	20%	33%	2%	2.4±2.5*
Schwann	RITA	60±10	12%	15%	54±11‡	6%	NR	NR	60±10	14%	17%	53±11‡	7%	NR	NR
[9]	RA	62±10	25%	37%	49±10‡	18%			58±10	13%	18%	52±10‡	8%		
Shi	RITA	60±10	8%	13%	23%	3%	NR	NR	63±9	11%	19%	23%	3%	NR	NR
[10]	RA	68±10	25%	30%	27%	5%			63±10	11%	18%	24%	4%		
Tranbaugh	RITA	66±11	29%	35%	46±15‡	8%	3%	NR	61±11	23%	36%	48±14	10%	2%	NR
[11]	RA	58±8	17%	38%	48±13‡	19%	2%		60±8	22%	37%	47±14‡	10%	2%	

Tsuneyoshi	RITA	68±8	19%	55%	3%	2%	NR	1.56†	68±10	19%	53%	2%	2%	NR	1.64†
[12]	RA	69±11	23%	46%	2%	3%		1.57†	68±10	25%	45%	1%	2%		1.61†

* Euroscore; †STS score; ††Percentage of patients aged ≥75; ‡ mean left ventricular ejection fraction

RITA: right internal thoracic artery; RA: radial artery; DM: diabetes mellitus; LVD: left ventricular dysfunction (different definition adopted); COPD: chronic obstructive pulmonary disease; RD: renal failure (different definition adopted); NR: not reported

Figure legend

Figure 1. Flow chart for study selection

Figure 2. Forest plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on late mortality across individual study and by means of pooled estimate.

Figure 3. Forest plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on operative mortality (A), incidence of sternal wound complication (B) and repeat revascularization (C) across individual study and by means of pooled estimate.

Figure 4. Forest plot of the leave-one-out sensitivity analysis (left) and the radial plot (right) comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on late mortality.

Supplementary Figure 1. Funnel plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on late mortality

Supplementary Figure 2. Funnel plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on operative mortality (A), incidence of sternal wound complication (B) and repeat revascularization (C)

Supplementary Figure 3. Forest plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on operative mortality in propensity matching studies and the RAPCO trial across individual study and by means of pooled estimate.

Supplementary Figure 4. Forest plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on operative mortality in all unmatched populations.

Supplementary Figure 5. Forest plot comparing the effect of right internal thoracic artery (RITA) versus the radial artery (RA) on operative mortality according to the target (LCA: left coronary artery; RCA: right coronary artery)